Re: Analysis of Dioxin Cancer Threshold

Mackie et al. (2003) present an exploratory Monte Carlo meta-regression of selected cohort mortality and exposure data for three dioxin-exposed cohorts [National Institute for Occupational Safety and Health (NIOSH), Ranch Hand, and Seveso] as a critique of our earlier publication of a similar analysis (Kirman et al. 2000). Although we appreciate that our preliminary examinations of the cohort mortality dose–response data have been followed by more detailed analyses of these data (e.g., Crump et al. 2003), we disagree with a number of Mackie et al.'s procedures, assertions, and conclusions.

Mackie et al. (2003) assert that no weighting of the individual cohort data points is necessary and that a linear regression of the unweighted dose–response data is appropriate. We disagree. The data used in the regression analysis include observations obtained for groups ranging from 19 individuals (Ranch Hand Group R4) to 15,000 individuals (Seveso Zone R females). In an unweighted regression, dose–response information from these two groups is weighted equally, which is clearly inappropriate. Weighting by sample size, while relatively simplistic, eliminates the sensitivity of the regression results to either study size or data-grouping decisions of the study authors. For example, the unweighted fits by Mackie et al. would have been quite different if the results for women in Seveso Zone R had been reported for 789 groups of 19 individuals rather than one group of 15,000. The data are probably best analyzed using a Poisson regression. Estimators produced by maximizing the likelihood function in a Poisson regression are generally preferred over those produced by least squares based on their statistical properties, and the data are automatically weighted based on the expected number of deaths (highly correlated with population size). The results of a Poisson regression would be expected to be nearly identical to those obtained using a population-weighted least-squares regression (ongoing work confirms this).

The broad conclusion of Mackie et al. (2003) that the data provide no evidence of a threshold is based on analysis of only three of the five cohorts with available dose–response data. Further, the data used in their analysis do not reflect the most current mortality information available for two of the three included cohorts [NIOSH cohort, updated by Steenland et al. (2001); Seveso cohort, updated by Bertazzi et al. (2001)]. Mackie et al.'s conclusion of no evidence of a threshold seems unreasonable on the basis of this incomplete analysis. Crump et al. (2003) noted that the dose–response data from the manufacturing cohorts do not show any positive trend until groups with estimated doses well above current background exposures are included. Data from the Seveso cohort are consistent with this observation.

Finally, data from the occupational cohorts indicate an underlying elevation in cancer mortality independent of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure [standard mortality ratio between 115 and 120 at zero dioxin exposure (Crump et al. 2003; Starr 2001)], consistent with possible confounding by exposure to other chemicals in the workplace, elevated smoking rates, or other factors. In contrast, the data from the Seveso and Ranch Hand populations, with more appropriate control populations, do not show this underlying elevation at zero exposure. Combining these two groups of populations into a single meta-regression may result in spurious effects on the apparent shape of the dose–response curve unless this elevation is accounted for.

In this respect, we agree with Mackie et al. (2003) that the epidemiologic data must be analyzed carefully using appropriate statistical and commonsense approaches, and with an awareness of the strengths and weaknesses of the underlying data. However, we think additional work remains to be done to fully appreciate the implications of the available epidemiologic data for the cancer dose–response of TCDD in humans.

The authors declare they have no conflict of interest.

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Editor's note: In accordance with journal policy, Mackie et al. were asked whether they wanted to respond to this letter. They chose not to do so.

Exposure to Lead and an Old Way of Counting

We read with great interest the commentary by Jacobs et al. (2003) on the high cost of improper removal of lead-based paint and would like to address two issues, both related to the monitoring of lead-based paint. The first is the importance of animal sentinels and the second is the potential of the capture–recapture method (CRM) (also called the mark–recapture method) for determining the number of homes with lead-based paint.

The commentary by Jacobs et al. (2003) addresses issues and concerns related to cost when lead-based paint removal is performed improperly. The case study referenced by Jacobs et al. first arose from the discovery that the family pet, a dog, died from apparent lead poisoning. Discovery of lead poisoning through a family pet has been previously reported (Dowsett and Shannon 1994), and some have suggested that pets are good sentinels for poisoning of children (Berny et al. 1995).

A similar event took place in western Pennsylvania in the 1980s (Lange JH. Unpublished data): a homeowner reported that the family's dog was exhibiting unusual behavior. A veterinarian tested the dog and determined that it had lead poisoning. A water tower on property bordering the residence was being sandblasted and repainted, and sand had been distributed throughout the yard, with some inside the residence. The contractor had put a tarp barrier over the chain-linked fence as the only control measure to prevent spread of sand, dust, and lead-based paint. After the finding of lead poisoning in the dog, the single resident in this home was tested for blood lead; the resident also had lead poisoning (blood lead level by venous draw > 25 μg/dL).

Most home and building owners are not aware of the hazards of lead-based paint nor its presence (Lange et al. 1998). Thus, it is common that renovation, repair, and/or

demolition occur without implementation of lead-control or lead-safe practices (Lange et al. 1998; Lange and Thomulka 2000), with most never discovering the hazard or even being concerned (Lange et al. 1998).

Sentinel events identify potential areas of concern; however, they do not determine the magnitude of the problem. One of the difficulties in understanding the lead hazards is their magnitude (Jacobs et al. 2002). There is currently no good estimate for the number of homes having lead-based paint and the incidence and prevalence of lead-poisoned children and adults in most local areas. Accurate estimates of these parameters would better identify the extent of the problem in local communities. Why these estimates are not known is a result of the difficulty in collecting accurate data. However, a nontraditional environmental health method can be used for providing these estimates: the CRM (LaPorte et al. 1992; McCarty et al. 1993). The CRM has been used for decades by population ecologists and others who count wildlife (LaPorte et al. 1992). This method will allow sampling of the population, including homes with lead-based paint, to determine the incidence and prevalence at a fraction of traditional costs. To better identify the problems of lead, it is necessary to employ new and innovative methods such as the CRM.

With the CRM, population ecologists take a sample of fish, for example, from Lake Erie, and count them, tag them, and return them to the lake; then on the next day, they once again capture a sample of fish and identify the numbers of fish that were caught. Using a simple formula, such as the one presented, it is possible to estimate numbers of fish in the lake.

When estimating numbers of people with lead poisoning, we can use multiple sources of case ascertainment, including hospitals, laboratories, and schools. Each list represents a capture, and the duplicates on the lists represent the recaptures. We can use the same approach for estimating the number of houses with lead-based paint (i.e., the number of houses that might be contaminated). To do this, it would be necessary to obtain multiple incomplete listings of houses with lead-based paint from local agencies, the houses where lead poisoned children lived, surveys, and so on. The incomplete lists represent the captures, and the houses that appear on duplicate lists would represent the recaptures. Using a simple formula, we can obtain an estimate that controls for ascertainment.

$$N = \frac{(M+1)(n+1)}{(m+1)} - 1,$$

where N is the estimate of number, M is the number marked in the first sample, n is the number collected in the second sample, and m is the number of those marked in the second sample that were collected.

$$\mathrm{Var}(N) = \frac{(M+1)(n+1)(M-m)(n-m)}{(m+1)^2(m+2)}$$

$$95\%\ \text{confidence interval} = \pm 1.95\sqrt{\mathrm{Var}(N)}$$

Because some of the houses could be false positives, a random sample of the houses could be tested. Then the estimated count could be adjusted to ensure accuracy of identification on the lists.

The animal reports demonstrate the importance of sentinels for detecting lead poisoning in people. The use of the CRM illustrates a more effective method for determining the number of people who experience lead poisoning and the number of homes that contain lead-based paint. Such information will allow a more accurate assessment of the problem and the financial resources needed for control.

The authors declare a real, apparent, or potential conflict of interest as defined in EHP*'s Instructions to Authors.*

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Editor's note: In accordance with journal policy, Jacobs et al. were asked whether they wanted to respond to this letter. They chose not to do so.

Carbon Monoxide Exposure and Carboxyhemoglobin

Given recent survey data showing that physicians ask their patients about carbon monoxide less frequently than any other common environmental health hazard (Kilpatrick et al. 2002), I welcome your effort to increase awareness of CO by publishing the case report of Devine et al. (2002) documenting "MRI and Neuropsychological Correlates of Carbon Monoxide Exposure." But why did they include a table purporting to specify "Human responses and approximate ambient CO air levels at various carboxyhemoglobin concentrations" (Table 2; Devine et al. 2002)?

Devine et al. (2002) reported being unable to obtain any CO exposure data and did not even mention their patient's carboxyhemoglobin (HbCO) level, which they apparently saw no need to measure or even report. In fact, Devine et al. gave several reasons for not relying on HbCO, including (quoting Myers et al. 1998) that it is "of little value in diagnosing either acute or chronic CO poisoning."

Their Table 2 (Devine et al. 2002) is misleading because it does not specify the duration of CO exposure, air temperature, altitude, the initial HbCO level of those exposed, the level of physical exertion, smoking status, blood alcohol level, breathing rate, age, or any of the many other variables known to significantly influence the variety and severity of CO symptoms at any HbCO level.

Most misleading is that the table suggests that no symptoms of any kind—aside from angina in heart patients upon exertion—should be expected under 10% HbCO. *EHP* is just one of several journals that have recently published large studies of human CO exposure documenting that increases of just 1–2 ppm in average outdoor CO levels—well below those associated with any increase in HbCO—are more significantly associated with increasing asthma prevalence (Guo et al. 1999) and asthma attacks (Yu et al. 2000) than any other atmospheric pollutant including ozone and particulates.

Moreover, although Devine et al. (2002) referenced their Table 2 to "data from

O'Donoghue" (O'Dohoghue 1985), from which it was indeed copied, O'Donoghue's version does not cite any actual data but merely four other sources (Ginsberg 1980; Stewart 1975, 1976; Stewart et al. 1970). Although three of these contain similar HbCO tables, they also do not cite any relevant data, just other published sources.

I had to check 14 such references before I found what appears to be the original table—itself unreferenced—in a typewritten "Report of Investigations" published by the U.S. Bureau of Mines in 1923 (Sayers and Yant 1923), apparently without any external peer review. The table (Sayers and Yant 1923) was qualified with the phrase "in general" and was clearly not based on any actual human data or study. Given that the version published by Devine et al. (2002) is thus without any credible foundation, misleading in its content, and irrelevant to their reported case, I urge them to retract it from their otherwise excellent paper.

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Carbon Monoxide Exposure and Carboxyhemoglobin: Response from White et al.

In his letter, Donnay objects to the inclusion in our paper (Devine et al. 2002) of a table (Table 2) describing signs and symptoms associated with several levels of carbon monoxide exposure and carboxyhemoglobin (HbCO) blood saturation. This table presents a historical perspective on the known physical effects of CO. The information contained in it is very different from that summarized in the case report, which details subtle effects of chronic low-level CO exposure on behavioral and cognitive function. Our Table 2, which was not included in the initial submission of this paper to *EHP*, was added at the request of reviewers. It was felt that such a table would provide a comparison point regarding historical, longstanding beliefs about CO effects. In the case report, this knowledge is compared to more recent research and clinical reports of CO effects and their relationship to HbCO.

We do not see a compelling reason for retracting the table from the paper, especially given the context of our presentation on subtle effects of CO.

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